LAPLACE-TIMI 57 Primary Results

A Double-blind, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of a Monoclonal Antibody to PCSK9 in Combination with a Statin in Patients with Hypercholesterolemia

Robert P. Giugliano, MD, SM, FAHA, FACC

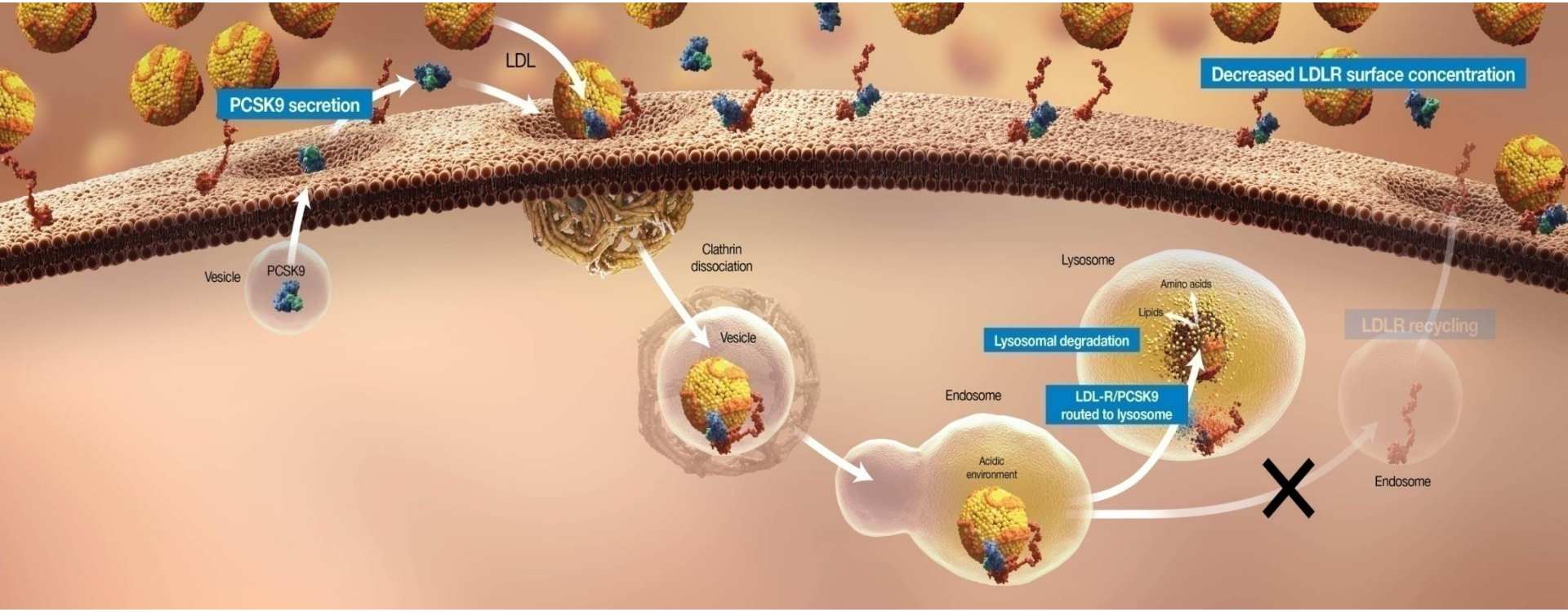
TIMI Study Group, Cardiovascular Division

Brigham and Women's Hospital

Harvard Medical School, Boston, MA

Supported by research grant from Amgen, Inc.

PCSK9 Regulates the Surface Expression of LDLRs by Targeting LDLRs for Lysosomal Degradation



AMG 145, a fully human monoclonal antibody that binds PCSK9, was well tolerated and lowered LDL in phase Ia and Ib studies

(Dias CS, JACC published online Oct 17, 2012. http://dx.doi.org/10.1016/j.jacc.2012.08.986)

Brown MS, et al. *Proc Natl Acad Sci U S A*. 1979;76:3330-3337.
Steinberg D, et al. *Proc Natl Acad Sci U S A*. 2009;106:9546-9547.
Goldstein JL, et al. *Arterioscler Thromb Vasc Biol*. 2009;29:431-438.

Qian YW, et al. *J Lipid Res*. 2007;48:1488-1498.
Horton JD, et al. *J Lipid Res*. 2009;50:S172-S177.
Zhang DW, et al. *J Biol Chem.* 2007;282:18602-18612.

Objectives

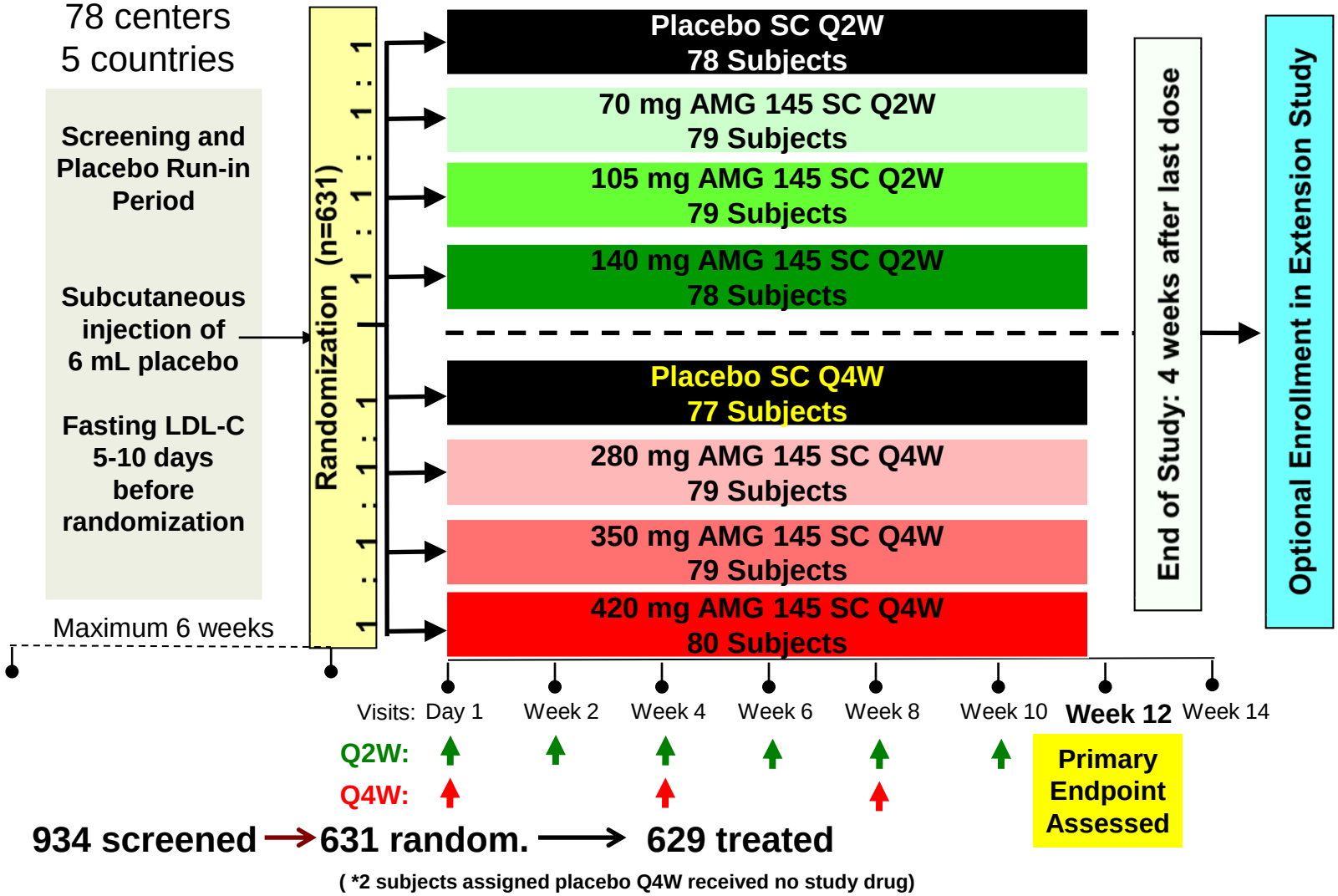
<u>Objectives</u>: To compare 12 weeks of AMG 145 (given SC Q2 or Q4 weeks) vs placebo in stable patients with hypercholesterolemia on a statin ± ezetimibe:

- Primary: % change in LDL-C*
- Secondary: changes in other lipoproteins
  pharmacokinetics/pharmacodynamics
  tolerability and safety

* measured using ultracentrifugation in a central core laboratory

Study Design

laplace–TIMI 57



Kohli P, et al. *Clin Cardiol*. 2012;35:385-391.

Major Entry Criteria

- **Age 18–80 years**
- **Stable dose of statin ± ezetimibe for 4 wks**
- **Fasting LDL-C ≥ 85 mg/dL**
- **Fasting triglycerides ≤ 400 mg/dL**
- **No other prescription lipid lowering therapy**
- **No recent ACS, revascularization, stroke**
- **No major comorbidities**

Randomization stratified by: 1) Baseline LDL (<130 vs ≥130 mg/dL)
2) Use of ezetimibe at baseline

Kohli P, et al. *Clin Cardiol*. 2012;35:385-391.

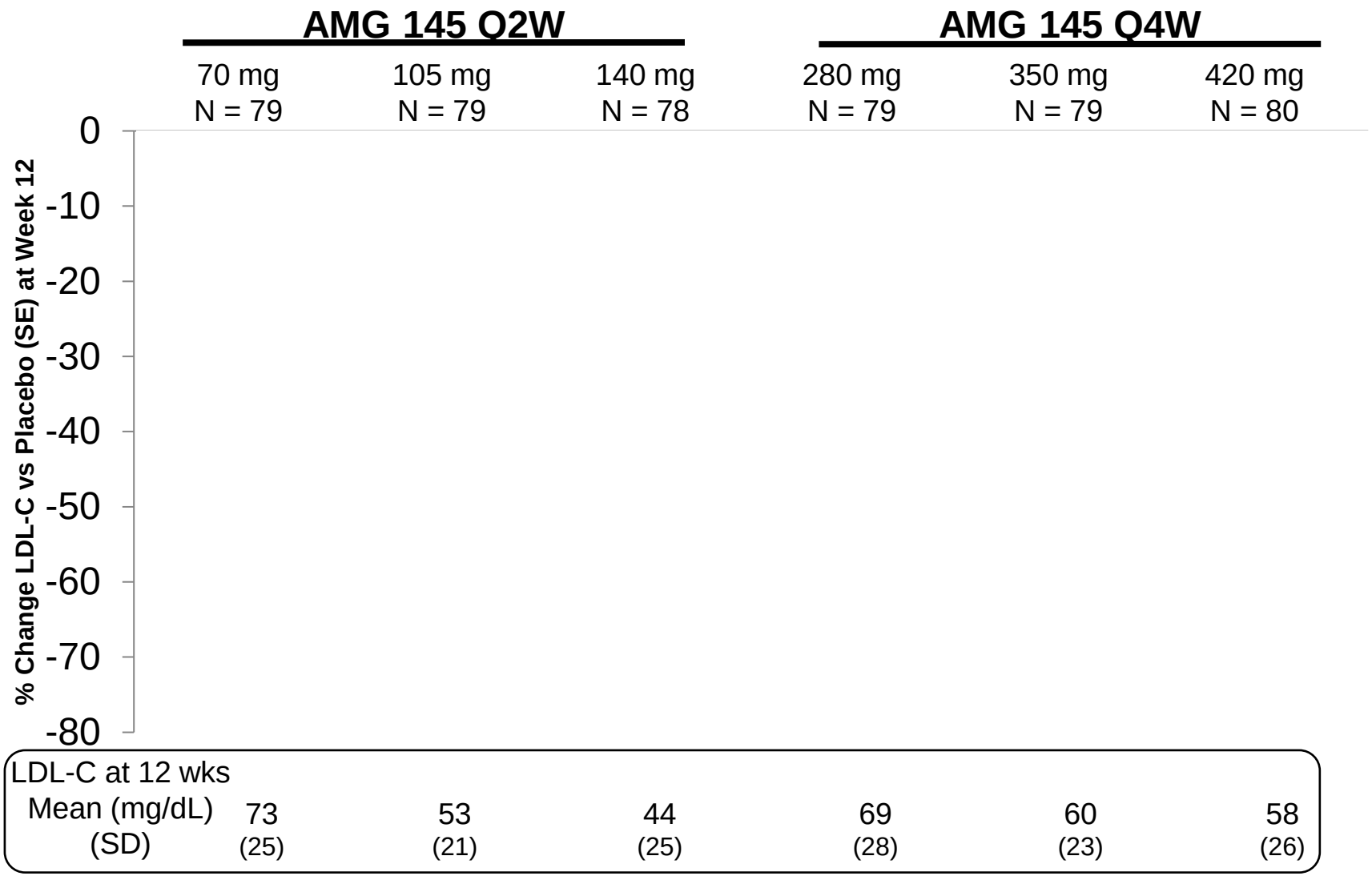
Baseline Characteristics

Characteristic	Placebo (N=157)	AMG 145 (N=474)
Age, years, mean (SD)	60 (9)	61 (10)
Sex, female, %	54%	50%
Race, white, %	94%	87%
LDL, mg/dL, mean (SD)	124 (29)	123 (27)
LDL < 130 mg/dL, %	66%	65%
Ezetimibe, %	10%	9%
Intensive statin regimen*, %	25%	31%
Diabetes mellitus, %	11%	18%
Body mass index (kg/M^2), mean (SD)	30 (5)	30 (6)
Coronary artery disease, %	27%	31%
Free PCSK9 (ng/mL), mean (SD)	450 (124)	443 (126)

P = NS for all comparisons

*rosuvastatin ≥20 mg, atorvastatin ≥40 mg, simvastatin 80 mg or ezetimibe + any statin

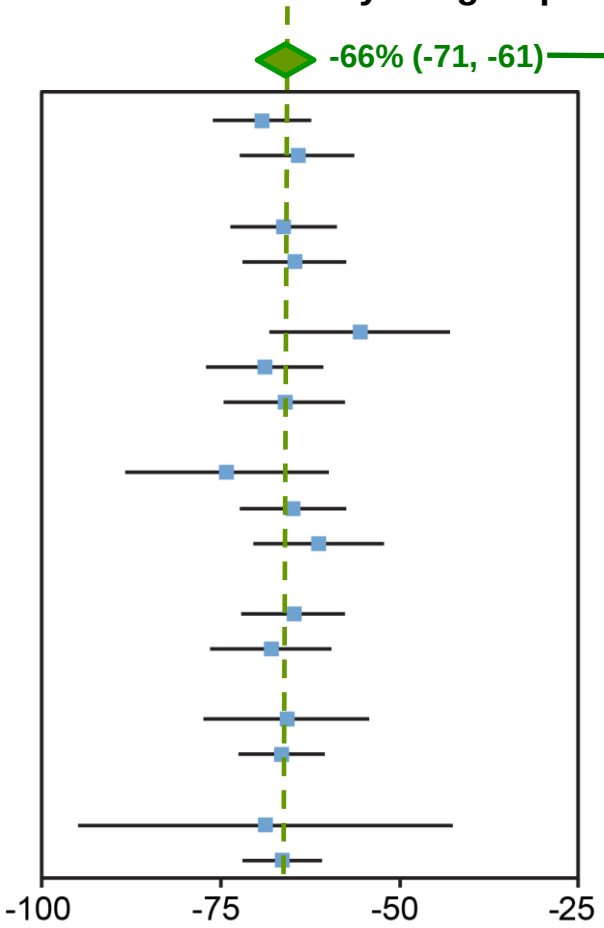
Primary Endpoint:
AMG 145 Reduced LDL-C at 12 wks



NOTE: LDL-C measured using ultracentrifugation in a central core laboratory

% Reduction in LDL with Top 2 AMG 145 Doses: Major Subgroups

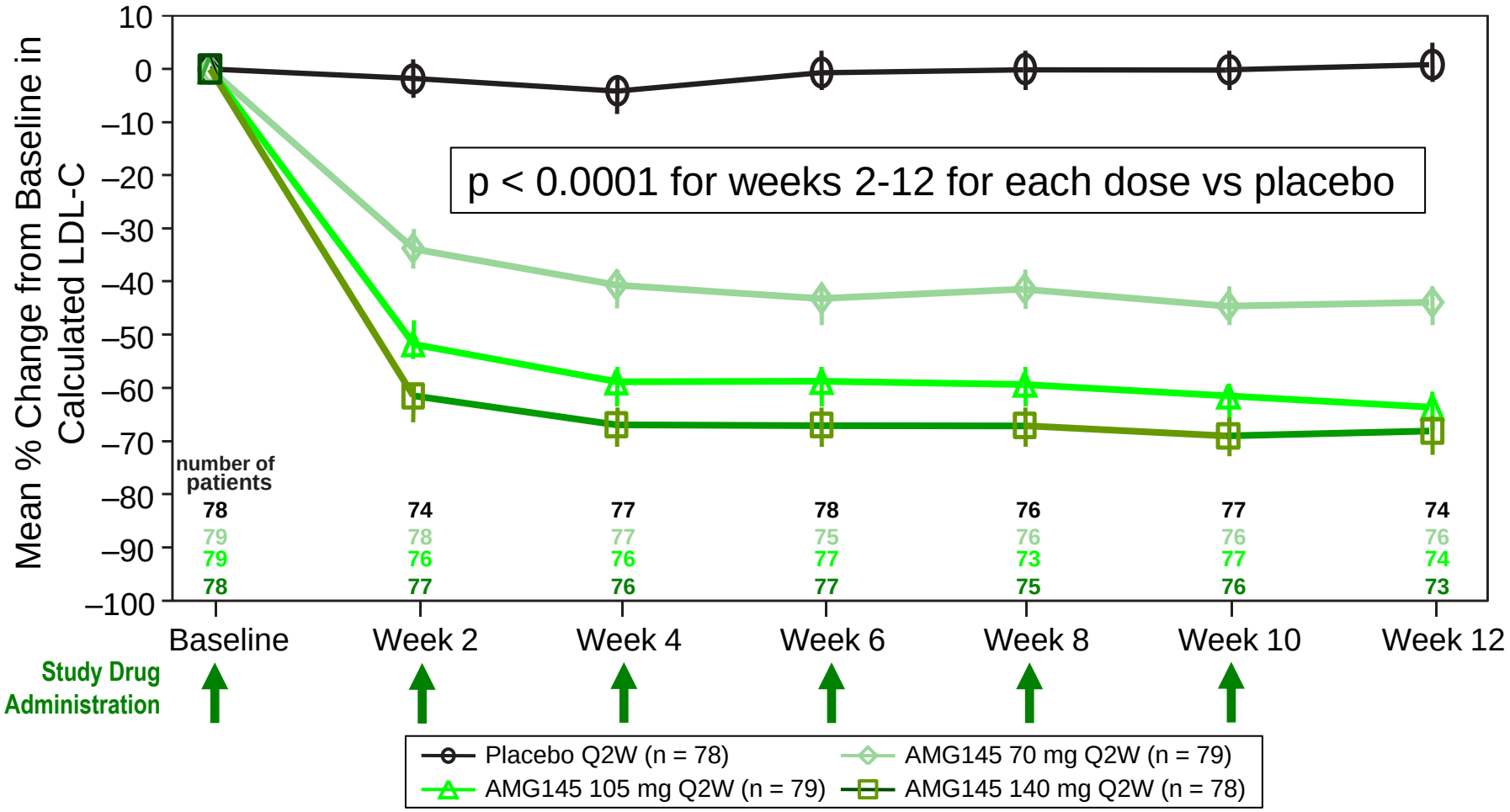
140 mg Q2W dose of AMG 145 reduced LDL at 12 weeks ranging from 56-74% in key subgroups



Baseline Characteristics
All patients
Men
Women
Age < 65 Years
Age ≥ 65 Years
BMI < 25 Kg/M2
BMI 25-30 Kg/M2
BMI ≥ 30 Kg/M2
Baseline UC LDL-C < 100 mg/dL
Baseline UC LDL-C 100-130 mg/dL
Baseline UC LDL-C ≥ 130 mg/dL
Baseline PCSK9 < median
Baseline PCSK9 ≥ median
Intensive statin regimen
Non-intensive statin regimen
Concomitant ezetimibe
No concomitant ezetimibe

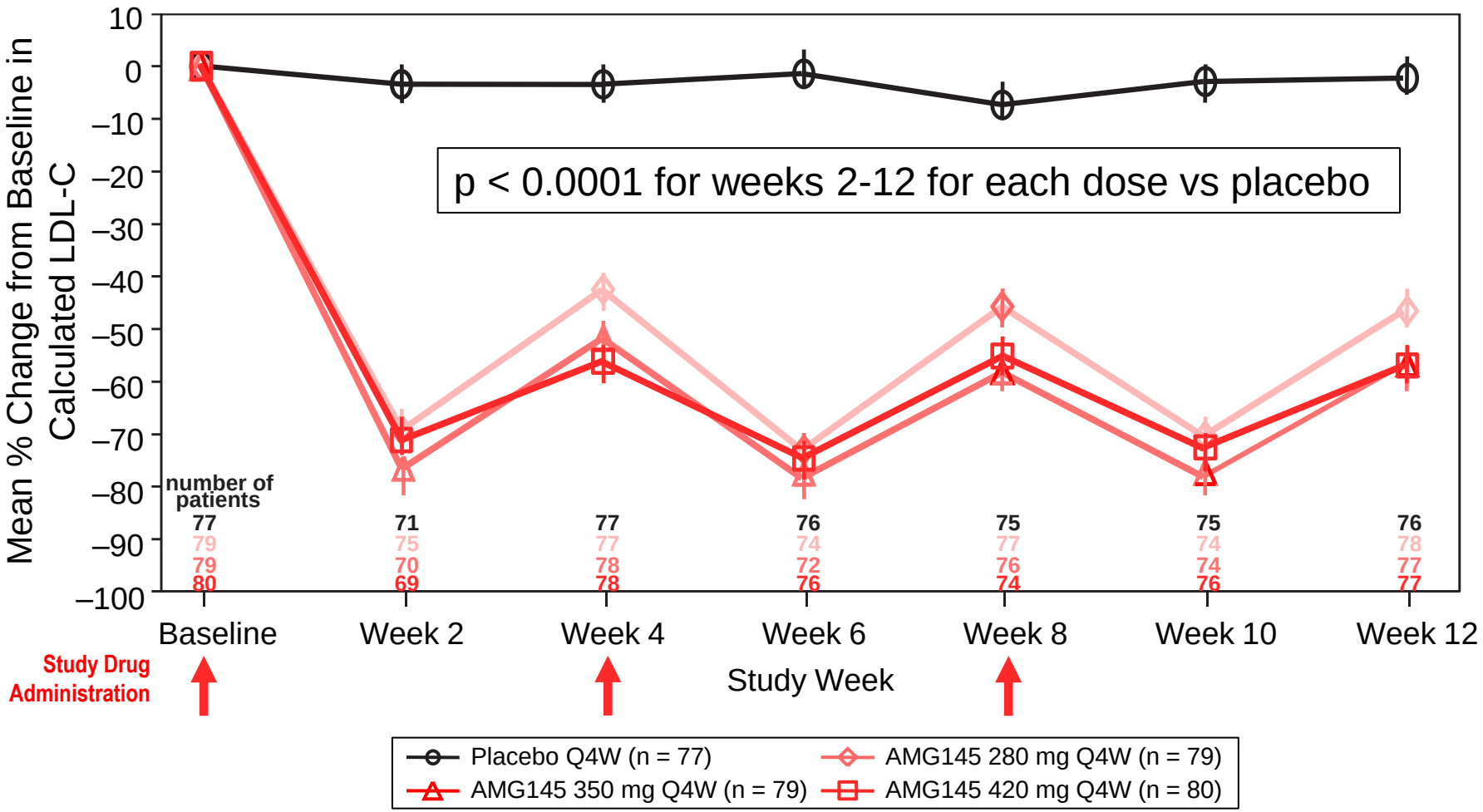
UC = Ultra centrifugation

AMG 145 Q2W Dose Response:
% Change in LDL-C Through 12 Wks



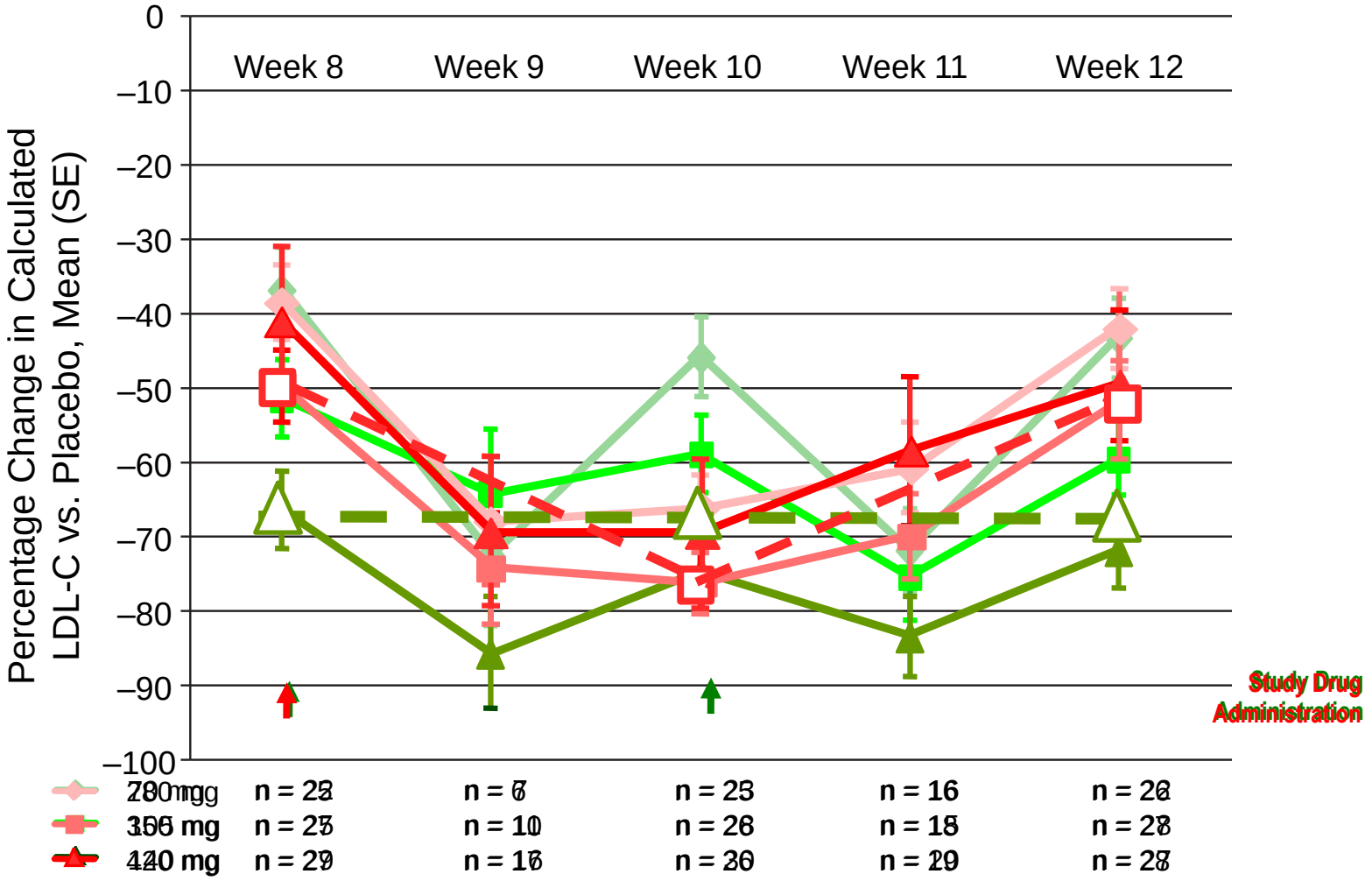
LDL-C calculated using the Friedewald equation

AMG 145 Q4W Dose Response:
% Change in LDL-C Through 12 Wks



LDL-C calculated using the Friedewald equation

AMG 145 Dose Response:
% Change in LDL-C Wks 8-12 (placebo adjusted)

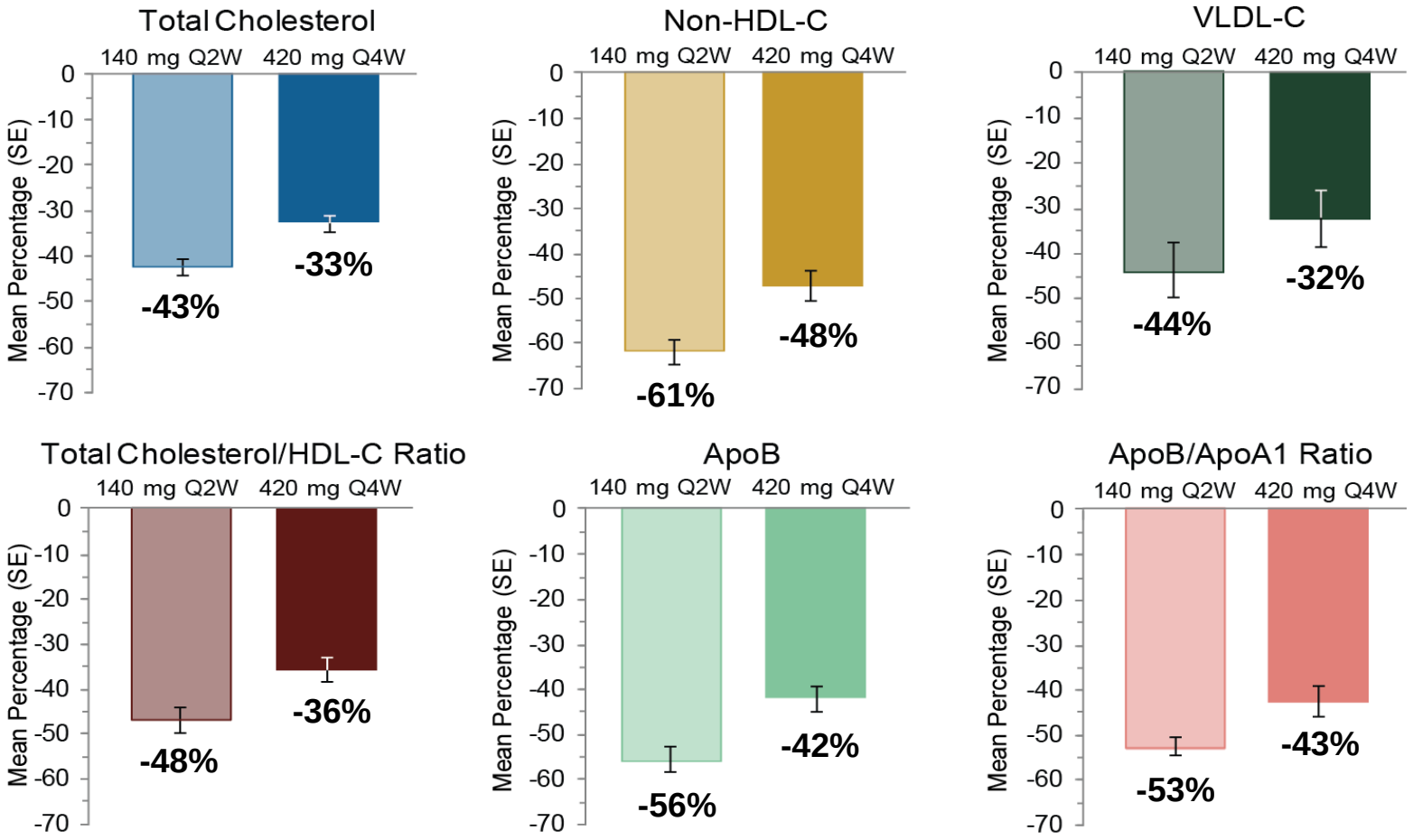


LDL-C calculated using the Friedewald equation

Secondary Results at 12 Wks with Top 2 AMG 145 Doses

laplace–TIMI 57

Treatment Effect vs. Placebo



***P* < 0.0001 versus placebo for all parameters**

Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error

Safety

laplace–TIMI 57

Adverse Events, Patient Incidence, n	Q2W Dose Groups				Q4W Dose Groups				
		AMG 145				AMG 145			
	Placebo N=78	70 mg N=79	105 mg N=79	140 mg N=78	Placebo N=77	280 mg N=79	350 mg N=79	420 mg N=80	Total N=629
Adverse events	33	41	52	43	38	45	48	48	348
Serious AE	4	0	1	4	0	2	2	2	15
Lead to drug DC	0	0	0	2*	0	0	0	0	2
Drug related AEs	7	4	9	4	4	6	7	9	50†
Lead to drug DC	0	0	0	0	0	0	0	0	0
Injection site rxn	2	1	1	0	1	2	3	1	11
AST or ALT >3x ULN	1	0	0	0	0	0	0	0	1
CPK >5X ULN	0	1	1	1	0	0	0	1	4**
CV events‡	1	1	0	4	0	1	1	0	8
Death	0	0	0	1	0	0	0	0	1

*Both events were reported as non-serious by the investigators.
†All 50 were reported as non-serious by the investigator and none led to discontinuation of drug
** All were asymptomatic ‡Acute coronary syndrome, coronary revascularization, TIA, congestive heart failure requiring hospitalization, or death

Summary & Conclusion

In patients with hypercholesterolemia on a stable regimen of statin ± ezetimibe, SC AMG 145 for 12 weeks:

- **Reduced LDL-C (ultracentrifugation) by up to 66% at the end of the dosing interval compared to placebo**
- **Reduced calculated LDL-C by up to 85% 1 week post dose**
- **Reduced total and non-HDL cholesterol, apo B, TC/HDL, Apo B/A1**
- **Well-tolerated with no dose-related increase in adverse events**

PCSK9 inhibition with AMG 145 offers a new paradigm for LDL-C reduction that warrants testing in a large, phase III cardiovascular outcomes trial

THE LANCET

Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging phase 2 study

*Robert P Giugliano, Nihar R Desai, Payal Kohli, William J Rogers, Ransi Somaratne, Fannie Huang, Thomas Liu, Satishkumar Mohanavelu, Elaine B Hoffman, Shannon T McDonald, Timothy E Abrahamsen, Scott M Wasserman, Robert Scott, Marc S Sabatine, for the LAPLACE-TIMI 57 Investigators**

***Lancet* 2012:380 (online first).**
Available on line at www.thelancet.com

Thank you to our investigators and coordinators, data safety committee members, clinical endpoint committee members, core laboratories, operational teams, monitors, and sponsor